Kinetics-Effect Relations of Insulin-Releasing Drugs in Patients With Type 2 Diabetes

Brief Overview

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Sulfonylureas and glinides have similar mechanisms of action but differ in receptor affinity and binding sites and in absorption and elimination rates. This promotes differences in potency, rate of onset, and duration of action. While prominent in single-dose studies, these differences have less importance during long-term sulfonylurea treatment: at ordinary dosages, rapid- and short-acting (glipizide) and slow- and long-acting (glyburide) sulfonylureas maintained continuously effective plasma levels and similar 24-h glucose control. Moreover, there was no difference in patient outcome between the first-generation sulfonylurea chlorpropamide and the second-generation glyburide in the U.K. Prospective Diabetes Study. However, the risk of long-lasting and hence dangerous hypoglycemia is higher with these two long-acting sulfonylureas. Conversely, this risk should be low with the short-acting glinides, but seemingly at the expense of less effective glucose control. The most important kinetics-effect relations are that hyperglycemia delays sulfonylurea absorption and that the sulfonylurea dose-response curve is bell shaped; continuous sulfonylurea exposure over a certain level (e.g., 10 mg glipizide) impairs rather than improves insulin and glucose responses to sulfonylurea (downregulation). Accordingly, a vicious circle may be established: unrelenting hyperglycemia may promote sulfonylurea maintenance dose increase, which increases hyperglycemia, promoting further dose increase and eventually therapeutic failure. Diabetes 53 (Suppl. 3):S151–S155, 2004

The pharmacodynamic characteristics of a therapeutic drug reside in its steric configuration, which determines its capacity to activate or inhibit a certain type of receptors or enzymes. However, its pharmacokinetic characteristics are instead determined by its physicochemical nature, i.e., whether and to what extent the compound is acidic or basic, hydrophobic (lipophilic) or hydrophilic (lipophobic), nonpolar (nonionized) or polar (ionized). Differences in these characteristics may lead to pharmacokinetic differences that explain why therapeutic drugs, despite identical mechanisms of action, may differ in clinical efficacy and/or safety.

Antihyperglycemic biguanides are an illustrative example. While metformin and phenformin have the same mechanism(s) of action, including a propensity to increase plasma lactate levels (1), phenformin is more prone to provoke serious and often fatal lactic acidosis (1). One reason for this is that the hydrophobic, weakly basic, nonpolar phenformin molecule has to be inactivated by aromatic oxidation via a hepatic cytochromal enzyme (CYP2D6) that displays monogenic polymorphism and is involved in the metabolism of a large number of hydrophobic, weakly basic drugs (2). Consequently, phenformin may accumulate at dangerous levels in subjects with genetically low activity of this enzyme. Dangerous accumulation might also occur if other drugs are given that compete with phenformin for binding sites on CYP2D6, e.g., some β-blockers (propranolol, metoprolol) and most calcium antagonists, antidepressants, and antipsychotics (2). The metformin molecule, on the other hand, is hydrophilic, strongly basic, and polar; hence it is not metabolized but excreted unchanged by the kidneys (1). Therefore, metformin-induced lactic acidosis can be avoided by dose reduction or disuse in patients with impaired renal function (1).

This example emphasizes the relevance of information on kinetics-effect relations of therapeutic drugs, and the current overview describes some of these relations among insulin-releasing compounds, i.e., sulfonylureas and meglitinide analogs (glinides).

SIMILAR PRINCIPAL MECHANISM(S) OF ACTION OF ORAL INSULIN-RELEASING DRUGS

Orally active sulfonylurea compounds (Fig. 1) have been used in the treatment of type 2 diabetes since the 1950s, following the serendipitous discovery a decade earlier that this kind of sulfonamides could reduce blood glucose levels (3). Subsequently, it was realized that the glucose-lowering effect is induced by stimulation of insulin release from the β-cells (3). Each antihyperglycemic sulfonylurea appears to initiate this process via certain binding sites (sulfonylurea receptors [SURs]) at the surface of the β-cells. These binding sites are linked to ATP-dependent...
K⁺ ion channels in the β-cell membrane (3). Sulfonylurea binding to SUR induces closure of the K⁺ ion channels, thereby preventing efflux of K⁺ ions from the β-cell cytoplasm. This leads to depolarization of the β-cell membrane, which evokes opening of voltage-sensitive calcium ion channels and increased calcium ion influx from the exterior. This influx promotes exocytosis of insulin (3). The endogenous ligands of the SUR (tentatively labeled endosulfines, by analogy with endorphins and endo-

Some years ago, it was discovered that also the nonsulfonylurea moiety of glyburide (HB 699, meglitinide) is able to stimulate in vitro insulin release from the β-cells, although its in vivo efficacy is only slight (4). This led to the assumption that the sulfonylurea moiety may be more important for SUR binding than for SUR activation (4). This, in turn, generated development of more potent insulin-releasing meglitinide analogs or glinides (4), such as repaglinide and nateglinide (Fig. 2). Like meglitinide itself, both of these nonsulfonylurea insulin releasers seem to function via the SUR-K⁺ ion channel complex, albeit with certain differences concerning binding sites (3–6).

CLINICAL EFFECT DIFFERENCES MAINLY RELATE TO DIFFERENCES IN PHARMACOKINETICS

While the principal mechanism of action thus appears similar for all therapeutically used sulfonylureas and glinides, there may nevertheless be prominent effect differences in relation to insulin and glucose levels due to pharmacokinetic differences (i.e., in receptor affinity and in absorption, distribution, metabolism, and excretion of the different compounds). These differences appear as differences in intrinsic activity and potency and in onset and duration of action. Moreover, as ATP-dependent K⁺ ion channels linked to SUR-like receptors are present not only in pancreatic β-cells but also in the brain, heart, vessels, and other tissues (3), different sulfonylureas and glinides may differ clinically even due to effects outside the pancreas. Chlorpropamide, for example, seems unique in promoting secretion of antidiuretic hormone and hence water retention (7). Some sulfonylureas might activate
The SUR affinity of the first-generation sulfonylurea (e.g., tolbutamide, chlorpropamide) is only about 1/1,000 of that of the second-generation sulfonfonylurea (e.g., glyburide, glipizide, and glimepiride) (3). This corresponds to similar differences in potency and efficacy: the effective doses and plasma levels of the second-generation sulfonylureas are in the range of 1–10 mg and 50–100 nmol/l, respectively, whereas those of the first-generation sulfonylureas are 250–3,000 mg and 50–100 µmol/l, respectively. Gliclazide, glibornuride, glicludone, and tolazamide are intermediate in both respects. The higher affinity and correspondingly lower effective plasma levels of the second-generation sulfonylureas might signify a lower risk of drug-drug interactions based on competition at plasma protein binding sites or hepatic enzyme sites (3). However, no relevant difference in glucose control and insulin levels between the various sulfonylureas has been observed in long-term comparative studies allowing for dosage adjustments, and there was no essential difference in outcome in the UKPDS between first-generation chlorpropamide and second-generation glyburide (12).

RATES OF ABSORPTION AND ONSET OF ACTION
Single-dose studies have shown considerable differences in the rates of absorption of glinides and different sulfonylureas, and the rates of onset of action differ accordingly (3,4) in the following approximate order (most rapid > least rapid): nateglinide > repaglinide > glipizide, glimepiride, gliclazide > tolbutamide, glyburide (micronized formulation) > chlorpropamide, glyburide (nonmicronized formulation). Accordingly, the glinides and the most rapid-acting sulfonylureas offer the apparent advantage of better restoration of the acute (first-phase or postprandial) insulin response to a meal, especially if the drug is ingested in due time before the meal (3,4,13–15). However, this advantage becomes negligible during long-term therapy; at steady state, glipizide and glyburide yield virtually identical 24-h glucose levels (16; see also below).

ELIMINATION, DURATION OF ACTION, GLUCOSE CONTROL, AND RISK OF LONG-LASTING HYPOGLYCEMIA
Most sulfonylureas are hydrophobic, weak acids and are mainly, if not exclusively, eliminated by metabolic transformation (3). The most prominent exception is chlorpropamide, which is more hydrophilic and is partially eliminated by renal excretion without preceding metabolic transformation. Hence, its effect may be prolonged in patients with renal impairment (3). Some sulfonylureas have active metabolites (e.g., glyburide) whose two-polar, hydroxylated metabolites are active in humans, and like chlorpropamide, may accumulate in subjects with renal impairment, thus adding to the duration of action of this drug (17,18).

The glinides, particularly nateglinide, have much shorter elimination half-lives than the sulfonylureas (4,14,15). This should reduce the risk of long-lasting hypoglycemia but should also diminish the duration of glucose reduction. So far, there are no randomized, controlled long-term clinical outcome studies comparing a sulfonylurea and a glinide. However, both nateglinide and repaglinide are mainly recommended for use in combination with metformin, acarbose, or a thiazolidinedione rather than as single-drug therapy (4).

The elimination half-lives differ pronouncedly between...
the sulfonylureas, that of glipizide being the shortest and that of chlorpropamide the longest (3). The duration of action in single-dose studies differs accordingly. Previously, glyburide seemed to be an exception, as its duration of action was long, despite a seemingly short half-life. However, improved high-pressure liquid chromatographic analyses have shown that its elimination half-life approaches 24 h (19). Moreover, its active metabolites may add to its long duration of action (18).

During long-term treatment, on the other hand, even glipizide promotes 24-h steady-state levels that are sufficient to maintain the same 24-h glucose control as long-acting glyburide (16; see also above). This appears true also for newer slow-release formulations of gliclazide and glipizide, as well as for the latest sulfonylurea, glimepiride. Nevertheless, the half-life differences between different sulfonylureas are clinically important, as the slow elimination of chlorpropamide and glyburide (plus its two active metabolites) makes these two sulfonylureas more liable than the others to promote long-lasting and hence dangerous and even fatal hypoglycemia (3). The short-lived glinides are assumed to carry the least risk of long-lasting hypoglycemia.

SULFONYLUREA PHARMACOKINETICS AND ETHNICITY
A comparison between Caucasian (in Sweden) and Chinese (in Hong Kong) patients with type 2 diabetes concerning the kinetics and effects of glyburide revealed minor differences in pharmacodynamics and none in pharmacokinetics (20). Hence, it was concluded that the same glyburide dosage principles could be used in Caucasian and Chinese patients with type 2 diabetes. Whether this applies to other sulfonylureas remains to be investigated.

HYPERGLYCEMIA DELAYS SULFONYLUREA ABSORPTION
As chronic hyperglycemia is pathognomonic for diabetes, it is important to know if hyperglycemia per se or the diabetic state otherwise influences the pharmacokinetics of insulin-releasing drugs. A study carried out in diabetic patients before and during insulin-induced euglycemia found that glyburide absorption was delayed during hyperglycemia (21). In addition, a study in healthy volunteers, in whom hyperglycemia was induced by glucose infusion, showed delayed absorption of glipizide, and the extent of this delay seemed to depend on the extent of hyperglycemia (22). Together, the studies indicate that hyperglycemia per se delays sulfonylurea absorption. In other words, worsening of glucose control may attenuate the acute insulin response to sulfonylureas. Moreover, efforts to compensate for this by increasing the sulfonylurea dose may be counterproductive, because sulfonylurea efficacy may be reduced by high dosage, as described in the next section.

REDUCED SULFONYLUREA EFFICACY FOLLOWING CONTINUOUS EXPOSURE TO HIGH SULFONYLUREA PLASMA LEVELS
The most important—but widely overlooked—aspect of the kinetics-effect relations of sulfonylureas is the fact that treatment promoting continuous exposure to high sulfonylurea plasma levels impairs rather than improves therapeutic efficacy, seemingly due to downregulation of SUR sensitivity. The initial experimental study suggesting this possibility (23) reported that the insulin-releasing effect of a single dose of a sulfonylurea (tolbutamide) vanished during chronic treatment with another sulfonylurea (tolazamide), even though glucose concentrations were maintained at the same levels by glucose infusion, and even though β-cell responsiveness to another insulin secretagogue (glucagon) remained intact. Moreover, the response to tolbutamide reappeared after cessation of tolazamide treatment. Subsequently, a nonrandomized clinical study showed that dose increase of glipizide from 15 to 25 mg/day, the increased sulfonylurea exposure being ascertained by higher glipizide plasma levels following the higher dose, was associated with impaired instead of improved glucose control in patients with type 2 diabetes (24). Furthermore (Fig. 3), a cross-over clinical trial in type 2 diabetic patients that compared 3-month treatment periods of once-daily placebo and 10, 20, and 40 mg glipizide in randomized order (the different degrees of sulfonylurea exposure being verified by measurements of plasma glipizide levels) showed that treatment with 10 mg/day was accompanied by higher insulin and lower glucose levels than 20 and 40 mg/day (25).

The hypothesis of sulfonylurea desensitization may draw further support from the observation that acute insulin release could be maintained in type 2 diabetic patients treated in order to achieve discontinuous sulfonylurea exposure (26). Moreover, a study on the most potent sulfonylurea, glimepiride, inferred that the desensitization is rapid (tachyphylaxis); it occurred within a week (27). Accordingly, there is evidence to assume that the dose-concentration-effect curve of sulfonylureas during chronic treatment is bell-shaped rather than sigmoidal. In other words, treatment with sulfonylureas may be counterproductive if the daily dosage exceeds a certain optimum. For glipizide, the optimum dose seems to be 10 mg/day (25), and the corresponding glyburide dose may be 7–10 mg (28). Indeed, exceeding these dose levels could establish a vicious circle: insufficient glucose control may lead to sulfonylurea dose increase, which may promote increasing hyperglycemia, which may cause further dose increase and eventually therapeutic failure. Hypotheti-
cally, the short half-lives of the glinides, especially nateglinide, would prevent occurrence of continuous exposure, but this remains to be experimentally verified.

CONCLUSIONS

Insulin-releasing drugs (i.e., sulfonylurea and glinides) display major differences in receptor affinity and hence in potency, as well as in rates of absorption and elimination and hence in rates of onset and duration of action. These differences are obvious in short-term studies but are less important during long-term treatment. Indeed, at ordinary dose levels, 24-h glucose control after 6 months was the same following treatment with rapid- and short-acting glipizide as with slow- and long-acting glyburide. Most important, there was no essential difference in patient outcome between the first-generation sulfonylurea chlorpropamide and the second-generation glyburide in the UKPD3. However, long-acting sulfonylureas, such as chlorpropamide and glyburide, seem to carry a greater risk of long-lasting and hence dangerous hypoglycemia. Conversely, this risk should be minimal with the short-acting glinides. On the other hand, their 24-h blood glucose reduction may be less than that of the sulfonylureas.

The most important kinetics-effect aspect of the sulfonylureas is that hyperglycemia delays sulfonylurea absorption and that treatment promoting continuous exposure to sulfonylurea concentrations over a certain level impairs rather than improves sulfonylurea efficacy. This may occur already at a glyburide or glipizide dosage exceeding 7–10 mg daily. Consequently, higher doses may initiate a vicious circle, leading to therapeutic failure. Accordingly, if a sulfonylurea dosage equivalent to 10 mg glipizide daily does not promote sufficient plasma glucose control, further dose increase should be avoided. Instead, addition of a non–insulin-releasing antihyperglycemic drug should be considered.

REFERENCES